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The impact of SARS-CoV-2 VOCs on clinical outcomes: an overview of reviews

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Background: Synthesizing data from existing literature is crucial for validating the robustness of associations, assessing data quality, and forming recommendations, especially given the vast amount of information available on SARS-CoV-2. This study aims to conduct an overview of reviews to evaluate the strength and validity of associations between VOCs and specific clinical outcomes in COVID-19 patients.

Methods: An overview of reviews according to the principles of PRIOR protocol was performed searching multiple databases in January 2024 and an updated search was conducted in MEDLINE database in June 2025. Peer reviewed systematic reviews considering two or more VOCs and reporting on clinical outcomes such as mortality, hospitalization, severe disease, admission to ICU, and mechanical ventilation were included. Data on study population and measures of association between clinical outcome and VOCs were considered. The quality of the studies was assessed through the AMSTAR-2 tool. Effect sizes and confidence intervals for each association between VOCs and clinical outcomes were reported. Subgroup analyses were performed where feasible. A citation matrix was used to assess the overlap between the included systematic reviews.

Results: Twelve studies were included in the review, with a total of 24 comparisons, primarily between Omicron and Delta variants (19/24). Omicron was consistently associated with better clinical outcomes compared to Delta. The confidence in the results of 10/12 studies was rated critically low. The overlap between the included reviews was minimal, with 10% having significant overlap (>15%).

Conclusion: Our overview of reviews shows the lower hazard on human health of the Omicron compared to Delta variant. However, the quality of the reviews included was generally low, prompting the need for more rigorous systematic reviews.

Systematic review registration: This overview of reviews was registered in PROSPERO, CRD42024500841; https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42024500841.

KEYWORDS

SARS-CoV-2, Omicron, Delta, VOCs, systematic reviews, COVID-19

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic represents one of the deadliest outbreaks of this century, causing an unprecedented global health crisis. Since its emergence in December 2019, the novel virus has caused approximately 778 million cases and at least 7.1 million deaths (1).

Following the first viral strain detected in Wuhan in 2019, multiple mutations have led to the emergence of variants of concern (VOCs) that circulated all over the world, changing the trajectory of the pandemic in terms of infections rates, severity of disease and death (2). Since then, the variants of concern have remained within the Omicron lineage, with JN.1 and KS.1 currently being the most relevant sublineages. These Omicron subvariants continue to drive new waves of infection, and their identification and tracking remain central to ongoing surveillance efforts, as highlighted by recent molecular and epidemiological studies (3, 4). On the other hand, earlier VOCs—Alpha, Beta, Gamma, and Delta—are no longer in significant circulation (3, 5). Together with the development and distribution of COVID-19 (coronavirus disease 2019) vaccines, a pivotal moment was the emergence of the Delta variant (B.1.617.2) noted for its high transmissibility and greater virulence than its predecessors. This VOC prevailed over other variants from late 2020 to early 2021 causing a significant spike in COVID-19 mortality. Another turning point was the subsequent emergence of the Omicron (B.1.1.529) and its subvariants, which are much more transmissible but less virulent than Delta (6).

Given the substantial and heterogeneous amount of evidence for clinical outcome associated with different VOCs, it is critical to understand how these variants impact COVID-19 clinical outcomes. This study aims to analyze systematic reviews, through an overview of reviews, that report on COVID-19 clinical outcomes stratified by VOCs.

Methods

Data sources and search strategy

A comprehensive literature search across several databases was conducted on January 18, 2024, with no language restrictions. The databases searched included Ovid MEDLINE 1946 to Present and Epub Ahead of Print, Ovid Embase (1974+), Web of Science Core Collection via Clarivate Analytics (1975+), and Scopus via Elsevier (1788+). Animal studies were excluded. The date limits were set between December 2022 and January 2024; an updated search was conducted in the MEDLINE database on June 10, 2025. The search strings were designed with a medical librarian with inputs from the study investigators. Controlled vocabulary terms were

supplemented with keywords. The search strategy is available in the [Supplementary File S1](#).

Systematic review selection and data extraction

An overview of reviews was conducted using multiple databases in January 2024, in accordance with the principles and definitions to Preferred Reporting Items for Overviews of Reviews (PRIOR); the protocol was prospectively registered with the PROSPERO database (CRD42024500841) (7).

The following inclusion criteria were applied: (i) peer-reviewed systematic reviews with or without meta-analysis, (ii) with data on at least two VOCs, and (iii) with one clinical outcome of interest associated with one or more VOCs. Clinical outcomes under evaluation included: mortality, hospitalization, intensive care unit (ICU) admission, invasive ventilation, and severe disease. Exclusion criteria were: (i) systematic reviews focusing on infants and subjects under 18 years of age, (ii) systematic reviews with insufficient details to extract data on the total number of patients included, (iii) systematic reviews without an effect size of association between the clinical outcome and the VOCs, and (iv) narrative reviews or reviews conducted without systematic methodology. Although we initially intended to investigate any clinical outcome, we subsequently decided to focus solely on key outcomes; this decision distinguishes this overview of reviews from the original PROSPERO protocol.

Citations were managed using a systematic review software (Covidence), and duplicates were removed. All titles and abstracts were independently screened by at least two of the three reviewers (FB, RF, and PR), followed by a full-text review of the selected articles conducted by the same reviewers. Discrepancies were resolved through discussion with a fourth reviewer (FF). Data extraction was performed independently by at least two reviewers out of four (FB, FF, RF, and PR) with discrepancies resolved with another reviewer (MP). The following data were collected: (i) systematic reviews' information: year of publication, source databases, and last date of literature search, (ii) included studies and patients' information: inclusion criteria, number of studies included, number of patients included, (iii) outcomes' information: VOCs considered, clinical outcomes considered, adjustments done, subgroup analyses, and effect estimates odds ratio (OR), risk ratio (RR) and hazard ratio (HR) with 95% confidence intervals (CIs).

Confidence in the results assessment

The quality of included systematic reviews was assessed using the AMSTAR-2 (MeaSurement Tool to Assess systematic Reviews 2) (AMSTAR-2). This tool consists of 16 items presented as questions, seven of which are considered critical. The overall confidence in the results of the reviews is rated as follows: (i) high, no or one non-critical weakness; (ii) moderate, more than one non-critical weakness; (iii) low, one critical flaw with or without non-critical weakness; (iv) critically low, more than one critical flaw with or without non-critical weakness (8). The AMSTAR-2 was filed independently by two of four authors (FB, RF, PR, and FF) and discrepancies resolved through discussion with another reviewer (MP).

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 19; VOCs, variants of concern; PRIOR, preferred reporting items for overviews of reviews; ICU, intensive care unit; AMSTAR-2, A MeaSurement Tool to Assess systematic Reviews-2; CI, confidence interval; GROOVE, Graphical Representation of Overlap for OVErviews; OR, odds ratio; RR, risk ratio; HR, hazard ratio; CCA, corrected covered area; CFR, case fatality rate.

Data analysis

We reported effect size measures with the corresponding 95% CI for each association between VOCs and the clinical outcome of interest. For the studies that directly compared two or more VOCs, the effect size measures considered included HR, OR and RR. We also planned to report the effect size measures for any subgroups analyzed within the studies.

A citation matrix visually organizing systematic reviews was constructed to assess their overlap using the Graphical Representation of Overlap for OVERviews (GROOVE) tool. This matrix quantifies overlap through the Corrected Covered Area (CCA), which is classified as very high (>15%), high (11–15%), moderate (6–10%), or slight (0–5%). The CCA is a validated method for measuring overlap between reviews, aiding in decision-making on managing overlap (9).

Results

We identified 3,547 articles: 1,253 from Scopus, 1,011 from Embase, 961 from PubMed and 322 from Web of Science. After deduplication, 1,940 articles underwent title and abstract screening resulting in 164 studies selected for full-text review. The entire screening process ultimately included 12 articles in the final review (Figure 1) (10–21).

Characteristic of included studies

The characteristics of the selected systematic reviews are summarized in Table 1. Among the 12 studies included, the majority used data published prior to 2023 (8/12, ~ 67%), and conducted a meta-analysis (9/12, ~ 75%). The number of total primary studies included in each systematic reviews ranged from 5 to 92. The VOCs examined were predominantly Omicron (12/12) and Delta (11/12). Four reviews focused exclusively on Omicron and Delta infections, one systematic review compared Omicron with all previous VOCs combined as one single group and one systematic review compared two different Omicron subvariants (BA1 and BA2). The study populations ranged from 8,850 to 670,913,033.

Clinical outcomes

Three studies compared mortality between Omicron and Delta in the overall population, and all of them reported a statistically significant lower odds or risk of mortality for patients infected with Omicron (Table 2), specifically RR 0.39 CI 95% 0.33–0.46, OR 0.33 CI 95% 0.16–0.67 (15) (4) and OR 0.34 CI 95% 0.25–0.46 (5, 6) (13, 15, 16). These results were also confirmed by the single systematic review adjusting for vaccination status (6), and by the subgroup analysis focusing on hospitalized patients and pregnant women (5, 7) (13, 16, 19). Only one review assessed the OR of mortality between Delta and pre-Delta in pregnant women, reporting lower odds in the pre-Delta era (7) (Table 2) (19).

Omicron was statistically associated with lower odds and risk of ICU admission and invasive ventilation compared to Delta in the overall population and in the analyses considered, including analysis restricted to hospitalized patients and pregnant women (Table 3).

Regarding hospitalization, Omicron was associated with lower odds compared to Delta. Two different reviews assessed the difference between Omicron BA1 and BA2 in the estimates of hospitalization, one adjusting for vaccination and the other for the prescription of Sotrovimab, and neither found significant differences (Supplementary Table S1) (13, 18).

However, it should be noted that in the latter review, only 5 papers were included and only one of them considered the difference in hospitalization between BA.1 and BA.2 (18).

As for severe disease, patients infected with Omicron were also less likely to develop it compared to those infected with Delta (Supplementary Table S2).

Confidence in the results

The overall confidence in the results was rated as high in only one systematic review (5) (16). Two were rated low (7, XX), and all the remaining results were rated critically low (4, 6, 7, 9–14). Regarding the critical items, only 3/12 studies reported clearly that the review methods were established prior to the conduct of the review (item 2); 11/12 had an adequate search strategy (item 4); 7/12 did not provide details or justifications for the excluded studies (item 7); 8/12 did not use or report satisfactory techniques to assess the risk of bias of the included studies (item 9); 5/12 did not consider this in their presentation of results (item 13). Only one out of eight systematic reviews that performed a meta-analysis explicitly stated in the protocol the principles guiding the decision to execute it (item 11), and only five of them considered the risk of publication bias in their results (item 15). The scores of individual studies are summarized in Table 4.

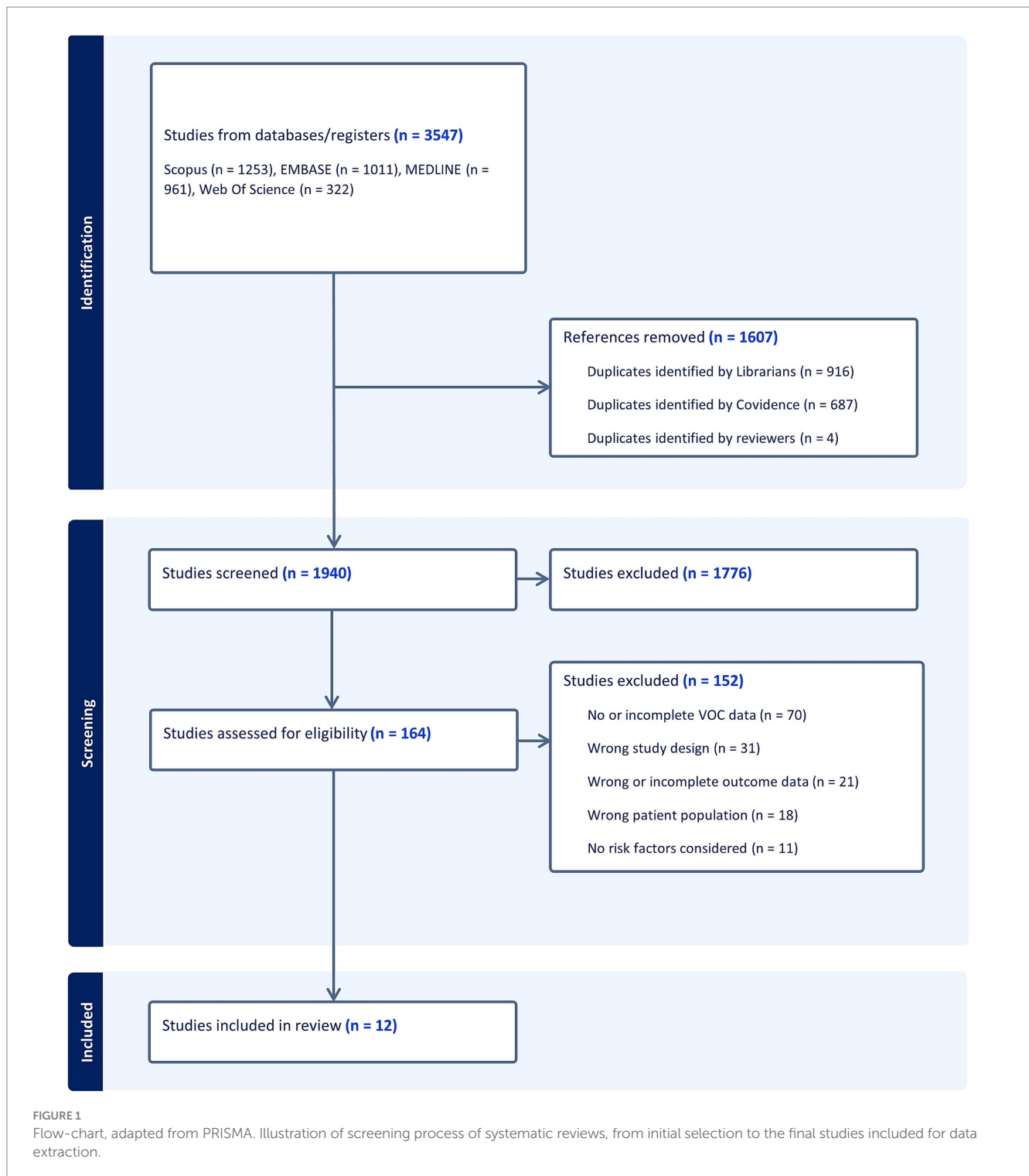
Overlap analysis

Overall, the overlap between the included reviews was generally low, with 51 out of 66 combinations showing slight overlap (<5%) (Supplementary Figure S1).

Discussion

Our systematic review shows that individuals infected with the SARS-CoV-2 Omicron variant experience a lower risk of adverse clinical outcomes compared to those infected with the Delta variant. Additionally, the overall quality of systematic reviews comparing hospital outcomes across multiple variants was generally low, and there was relatively low overlap among the systematic reviews included in our analysis.

The widespread distribution of COVID-19 vaccines and the emergence of the less virulent SARS-CoV-2 Omicron variant have significantly altered the pandemic's trajectory. A recent systematic



review, which examined the case fatality rate (CFR) of various SARS-CoV-2 variants across different continents, confirmed that Omicron poses a lower hazard compared to other variants (22).

Additionally, the reduced severity of Omicron infections may be due to its emergence 2 years into the pandemic and 1 year after the vaccination campaign began, by which time many individuals had likely acquired natural and/or vaccine-induced immunity.

Despite Omicron's lower mortality and other adverse outcomes compared to Delta, it remains a significant public health threat.

Data indicate that Omicron's hospitalization and mortality rates are comparable to, if not higher than, those of other endemic respiratory viruses such as influenza and respiratory syncytial virus (23, 24). Existing literature suggests that individual risk factors, such as male gender, age over 60 years, smoking, hypertension, diabetes, cancer, cerebrovascular disease, chronic kidney disease, chronic pulmonary disease, and chronic liver disease, may vary in their influence depending on VOCs, and their role on COVID-19 outcomes has been extensively studied (25).

TABLE 1 Characteristics of the 12 included studies in the overview of reviews.

First author, Year of publication	Last search	Source database	Meta-analysis	Inclusion criteria of the studies	Clinical outcomes considered	VOCs	N° of studies
Arabi et al. (20)	1st March 2022	PubMed, Medline, Embase, Scopus, Web of Science, Science Direct, MedRxiv, Lens.org	No	Omicron SARS-CoV-2 infected patients.	Hospitalization ICU admission Oxygen support IV Cardiovascular and hematological complications, Death	Omicron, Delta, Alpha, Beta, Wild Type	62
Arabi et al. (21)	6th March 2022	PubMed, Medline, Embase, Scopus, Web of Science, Science Direct, MedRxiv, Lens.org	No	Data on efficacy of previous SARS-CoV-2 infection vs Omicron infection.	SARS-CoV-2 reinfection or severe complications Duration of immunity	Omicron, Pre-Omicron	27
Deng et al. (19)	14th August 2022	PubMed, Embase, Web of Science, Science Direct, medRxiv, bioRxiv	Yes	Maternal or perinatal outcomes of SARS-CoV-2 infection. Virological data on SARS-CoV-2 VoCs available Epidemiological data SARS-CoV-2 VoCs available	ICU admission Maternal death Mild or moderate disease Severe or critical disease Oxygen support NIV IV ECMO Anti-SARS-CoV-2 treatments Placental abruption PPH Blood transfusion Cesarean section Preeclampsia or Eclampsia Preterm birth <37 week Newborn SARS-CoV-2 infection Stillbirth	Omicron, Delta, Gamma, Beta, Alpha	18
Du et al. (17)	20th July 2022	PubMed, Embase, ScienceDirect	Yes	Patients hospitalized Patients with long COVID-19 Virological data on SARS-CoV-2 VoCs available	Clinical symptoms PFT Chest CT Quality of life	Alpha, Beta, Gamma, Delta, Omicron, Wild Type	51
Kow et al. (15)	7th June 2022	PubMed, Web of Science, Scopus, Google Scholar, medRxiv, Research Square, SSRN	Yes	Delta vs. Omicron SARS-CoV-2 infected patients.	Mortality severe disease ICU admission IV	Omicron, Delta	12
Hu et al. (16)	10th November 2022	PubMed, Web of Science, bioRxiv, medRxiv	Yes	Delta vs Omicron SARS-CoV-2 infected patients	Hospitalization ICU admission IV Death	Omicron, Delta	33
Nguyen et al. (14)	31th March 2023	Pubmed, Google Scholar	Yes	All adult SARS-CoV-2 re-infected patients. Virological data on SARS-CoV-2 VoCs available	Hospitalization Severe disease Clinical symptoms	Alpha, Delta, Omicron, Other	26
Relan et al. (13)	31st May 2023	WHO COVID-19 Research database	Yes	Delta vs Omicron SARS-CoV-2 infected patients.	Hospitalizations ICU admission Oxygen support HFNC NIV IV Death	Delta, Omicron	42

(Continued)

TABLE 1 (Continued)

First author, Year of publication	Last search	Source database	Meta-analysis	Inclusion criteria of the studies	Clinical outcomes considered	VOCs	N° of studies
Reynolds et al. (12)	May 2023	PubMed, Medline OVID, Web of Science, CAB direct	No	Data on efficacy of COVID-19 vaccines vs SARS-CoV2 VoCs infections available	Hospitalization Severe disease Death	Alpha, Delta, Omicron	92
Yu et al. (10)	18th April 2022	PubMed	Yes	Delta vs Omicron SARS-CoV-2 infected patients	Symptomatic infection Severe disease	Omicron, Delta	68
Yuan et al. (11)	1st February 2022	PubMed/MEDLINE, Embase, Web of Science (WOS), and China National Knowledge Infrastructure (CNKI)	Yes	SARS-CoV-2 infected patients	cCHR cCFR HFR HIR	Alpha, Beta, Delta, Omicron	13
Drysdale et al. (18)	3rd November 2022	MEDLINE, Embase, LitCOVID, Cochrane COVID-19 Study Register, Econlit, ArRxiv, BioRxiv, ChemRxiv, MedRxiv, Preprints.org, ResearchSquare, SSRN, Conference abstracts (IDWeek, ERS, ECCMID)	No	SARS-CoV-2 infected patients who received Sotrovimab during BA.1 variant predominance	Hospitalization, ICU admission, ED visit, respiratory support, COVID-19 progression, mortality	Omicron BA.1, Omicron BA.2	5

VOCs, variants of concern; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; IV, invasive ventilation; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; ECMO, Extracorporeal Membrane Oxygenation; PPH, post partum hemorrhage; PFT, pulmonary function tests; CT, computed tomography; cCHR, confirmed case-hospitalization risk; cCFR, confirmed case-fatality risk; HFR, hospitalization-fatality risk; HIR, hospitalization ICU-risk; ED, emergency department.

TABLE 2 Estimates of mortality associated with different VOCs, including effect sizes and mortality estimates, extracted from the selected systematic reviews.

VOCs	No of studies	No of patients	Estimates (95% CI)	Delta risk (n/N), %
Overall population				
Omicron vs. Delta (Kow, 2023)	4	70.038	OR 0.33 (0.16–0.67)	611/42.238, 1.45%
Omicron vs. Delta (Hu, 2023)	13	5.371.394	OR 0.34 (0.25–0.46)	54.044/225.189, 23.99%
Omicron vs. Delta (Relan, 2023)	18	1.285.786	RR 0.39 (0.33–0.46)	37.897/391.155, 9.69%
Adjustments				
Omicron vs. Delta, [adjusted for vaccination] (Relan, 2023)	9	1.085.771	RR 0.39 (0.32–0.47)	1.836/246.049, 0.75%
Subgroups				
Omicron vs. Delta [only hospitalized] (Hu, 2023)	8	301.309	OR 0.69 (0.58–0.82)	18.402/171.663, 10.72%
Omicron vs. Delta [only pregnant women] (Deng, 2022)	3	1.050	OR 0.22 (0.06–0.82)	127/27.736, 0.46%
pre-Delta vs. Delta [only pregnant women] (Deng, 2022)	6	119.732	OR 0.28 (0.22–0.37)	107/91.996, 0.12%

Overlap by means of GROOVE tool: Kow 2023 and Hu 2023: 16.7%; Kow 2023 and Relan 2023: 15%; Hu 2023 and Relan 2023: 18.5%; Relan 2023 and Deng 2022: 2%; Hu and Deng 2022: 0%. VOCs, variants of concerns; CI, confidence interval; n/N, total number of patients with ICU admission or invasive ventilation/overall number of patients in the delta group; OR, odds ratio; RR, risk ratio.

Moreover, it is well-established that the number of comorbidities also impacts COVID-19 infection outcomes, though their influence may differ by VOCs. Specifically, a study by Piralla et al. found that ICU patients with Omicron were more likely to have three or more comorbidities compared to those with Delta, indicating that Delta infections are more aggressive and require fewer underlying conditions to become severe (26).

Unfortunately, our review could not determine the differential impact of individual risk factors on clinical outcomes across VOCs.

Beyond the primary findings of our overview of reviews, one result we consider equally important yet troubling is the overall poor quality of the systematic reviews analyzed. From our perspective, systematic reviews with meta-analyses represent a

TABLE 3 Estimates of ICU admission associated with different VOCs, including effect sizes and mortality estimates, extracted from the selected systematic reviews.

VOCs	No of studies	No of patients	Estimates (95% CI)	Delta risk (n/N), %
ICU admission				
Overall population				
Omicron vs. Delta (Hu, 2023)	13	2,977,877	OR 0.27 (0.20–0.38)	57,769/1,574,082, 3.67%
Omicron vs. Delta (Relan, 2023)	15	217,561	RR 0.46 (0.37–0.57)	22,181/151,323, 14.65%
Subgroups				
Omicron vs. Delta [only hospitalized] (Hu, 2023)	8	301,309	OR 0.61 (0.50–0.76)	35,534/171,663, 20.69%
Omicron vs. Delta [only pregnant women] (Deng, 2022)	2	N/A	OR 0.15 (0.02–0.97)	236/27,427, 0.86%
pre-Delta vs. Delta [only pregnant women] (Deng, 2022)	5	N/A	OR 0.37 (0.21–0.67)	468/91,657, 0.51%
Invasive ventilation				
Overall population				
Omicron vs. Delta (Hu, 2023)	9	484,717	OR 0.32 (0.18–0.57)	9,377/238,610, 3.93%
Omicron vs. Delta (Relan, 2023)	11	30,852	OR 0.41 (0.29–0.57)	2,071/20,566, 10.07%
Subgroups				
Omicron vs. Delta [only hospitalized] (Hu, 2023)	7	300,234	OR 0.61 (0.47–0.78)	18,639/170,997, 10.90%
Omicron vs. Delta [only pregnant women] (Deng, 2022)	2	798	OR 0.12 (0.02–0.92)	49/27,085, 0.18%
pre-Delta vs. Delta [only pregnant women] (Deng, 2022)	3	118,034	OR 0.60 (0.42–0.84)	93/90,549, 0.10%

Overlap by means of GROOVE tool: Hu 2023 and Deng 2022: 0%; Hu 2023 and Relan 2023: 18.5%. VOCs, variants of concerns; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RR, risk ratio; N/A, not available; n/N, total number of patients with ICU admission or invasive ventilation/overall number of patients in the delta group.

TABLE 4 Assessment of methodological quality and confidence in the results of the included systematic reviews using the AMSTAR-2 tool (critical domains in bold).

	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15*	16	Overall rating of quality
Arabi_1 (305), 2023	Y	PY	N	PY	Y	Y	N	N	N	N	NA	NA	N	N	NA	Y	Critically low
Deng, 2022	Y	Y	N	PY	Y	Y	PY	PY	N	N	N	Y	Y	Y	Y	Y	Critically low
Du, 2022	Y	Y	N	PY	Y	Y	PY	PY	PY	N	N	Y	Y	Y	Y	Y	Low
Arabi_2 (483), 2023	Y	PY	N	PY	Y	Y	N	N	N	N	NA	NA	N	N	NA	Y	Critically low
Kow, 2023	N	PY	N	PY	Y	Y	N	Y	N	N	N	N	N	Y	N	Y	Critically low
Hu, 2023	Y	Y	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	High
Nguyen, 2023	N	N	N	PY	Y	Y	PY	N	N	Y	N	Y	N	N	Y	Y	Critically low
Relan, 2023	Y	PY	Y	PY	Y	Y	N	PY	Y	Y	N	Y	Y	Y	N	Y	Critically low
Reynolds, 2023	Y	N	Y	PY	Y	Y	N	PY	N	N	NA	NA	Y	Y	NA	Y	Critically low
Yuan, 2023	N	N	N	N	Y	Y	Y	PY	N	N	N	N	N	N	N	Y	Critically low
Yu, 2023	Y	PY	Y	PY	Y	Y	N	PY	N	Y	N	N	Y	Y	Y	Y	Critically low
Drysdale, 2024	Y	PY	N	PY	Y	N	N	PY	Y	Y	NA	NA	Y	Y	NA	Y	Low

Domains (critical domains in bold): (1) PECO components; (2) **Protocol**; (3) Study design explanation; (4) **Comprehensive search strategy**; (5) Duplicate study selection; (6) Duplicate data extraction; (7) **Details of excluded studies**; (8) Descriptions of included studies; (9) **Risk of Bias assessment**; (10) Funding source; (11) **Appropriateness of meta-analysis**; (12) Meta-analysis RoB studies; (13) **Consideration of RoB for results**; (14) Heterogeneity; (15) **Meta-analysis, publication bias**; (16) Reports conflict of interest. PECO, population-exposure-comparator-outcome; RoB, risk of bias; Y, yes; PY, partially yes; N, no; NA, not available.

powerful tool for scientific dissemination, and the rigor we expect is crucial for acquiring fundamental information. It is not surprising, though disappointing, that some of this rigor may have been compromised during the early stages of the COVID-19 pandemic. However, we believe that strictly adhering to scientifically rigorous checklists for proper systematic review

methodology is a responsibility we, as researchers, owe to the common good—that is, the advancement of knowledge in our challenging scientific field. This goal should not be lost even in emergency settings like pandemics, where frameworks for evidence synthesis programs exist (27, 28). Our review identified several recurrent methodological flaws across the included studies, with some of the most relevant being the lack of information on excluded studies, insufficient risk of bias assessment, and limited consideration of bias in the interpretation of results—all of which are classified as critical domains in the AMSTAR-2 checklist. Future systematic reviews on this topic should aim to address these and other methodological weaknesses more rigorously, in order to acquire more reliable information in the future.

Some limitations must be considered. First, the focus on systematic reviews may have limited our findings by excluding individual studies. Second, most included reviews compared Omicron to Delta, while few addressed the various Omicron sublineages that currently dominate the COVID-19 landscape, and no comparisons with earlier variants were available in the selected papers. However, these findings reflect the scope and limitations of the existing literature at the time of our search, as well as the eligibility criteria applied in our review.

Third, omicron is markedly more transmissible and less virulent than previous VOCs, and underreporting remains a common issue.

Finally, our study could not assess the potential impact of other characteristics affecting clinical outcomes, such as vaccination status, type of treatment, and comorbidities; however, few of the included studies reported adjustments and subgroup analyses.

To our knowledge, this is the first overview of reviews to systematically synthesize evidence on COVID-19 clinical outcomes by variant, with particular attention to the methodological quality of the included systematic reviews.

Despite its limitations, we believe our work offers meaningful contributions, offering a valuable foundation for future research and informing public health strategies in the face of an evolving SARS-CoV-2 landscape.

Conclusion

Our overview of reviews highlights the lower health risk posed by the Omicron variant but also reveals a lack of high-quality systematic reviews regarding the role of comorbidities and other risk factors in COVID-19 progression. More research is needed to understand how different comorbidities influence severe COVID-19, and rigorous systematic reviews are essential to fill this gap and to aid in developing targeted clinical guidelines and public health policies.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

Author contributions

FF: Data curation, Conceptualization, Writing – original draft, Writing – review & editing. RF: Writing – review & editing, Data curation. PR: Data curation, Writing – review & editing. FB: Data curation, Writing – review & editing. DH: Writing – review & editing. TM: Data curation, Writing – review & editing. TN: Methodology, Writing – review & editing. AB: Writing – review & editing. AG: Writing – review & editing. MP: Writing – review & editing, Conceptualization, Visualization, Formal analysis, Validation, Methodology. MC: Validation, Visualization, Formal analysis, Conceptualization, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2025.1624459/full#supplementary-material>

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